

The Synthesis of Derivatives of 3,4-Benzpyrene

1. Some Modifications of the Synthesis of 3,4-Benzpyrene from Pyrene
2. 4',5-Dimethylene-3,4-Benzpyrene
3. Methyl Derivatives of 3,4-Benzpyrene. The Willgerodt Reaction on some 3-Acylpyrenes

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN THE UNIVERSITY OF MICHIGAN

By
Marvin Carmack
1940

Easton, Pa.
Mack Printing Company

[Reprinted from the Journal of the American Chemical Society, 63, 1682, 1685, 2494 (1941).]



[Reprinted from the Journal of the American Chemical Society, 63, 1682 (1941).]

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Some Modifications of the Synthesis of 3,4-Benzpyrene from Pyrene

BY W. E. BACHMANN, MARVIN CARMACK¹ AND S. R. SAFIR

In the Cook and Hewett² synthesis of the carcinogenic hydrocarbon 3,4-benzpyrene, pyrene is condensed with succinic anhydride, the resulting β -3-pyrenoylpropionic acid (I) is reduced to γ -3-pyrenylbutyric acid, the latter is cyclized to 4'-ketotetrahydrobenzpyrene and the ketone is converted to the hydrocarbon. In this paper we are reporting some modifications of this synthesis which we found useful for preparing the hydrocarbon.³

Usually β -aroylpropionic acids are reduced by the Clemmensen method, but Cook and Hewett² and also Martin⁴ have shown that the method fails with β -3-pyrenoylpropionic acid. Neither the acid nor its ester was reduced by zinc and hydrochloric acid with or without the use of toluene, and the employment of acetic acid in the reducing mixture resulted in the formation of resinous products. Although Cook and Hewett succeeded in reducing the keto acid by means of zinc and

alkali, a reaction which Vollmann, Becker, Corell and Streeck⁵ carried out most successfully in an autoclave at 80–100 atmospheres pressure, it seemed desirable to reinvestigate the Clemmensen method because of the simplicity of the procedure employed and because it was of interest to know whether conditions could be found for reducing the compound by this method. After considerable experimentation, it was found that the keto acid is reduced to γ -3-pyrenylbutyric acid when a mixture of chlorobenzene, xylene and acetic acid is used in the Clemmensen mixture. The yields of fairly pure reduced acid varied from 68 to 84% and depended chiefly on the amounts being reduced. It is noteworthy that under the conditions employed the reaction proceeds extremely rapidly for a Clemmensen reaction in spite of the slight solubility of the keto acid; thus, on a 2-g. run a 70% yield of the reduced acid was obtained when only two hours were allowed for the reaction.

A small amount of a rather insoluble colorless solid is formed as a by-product in the reaction;

(1) From the Ph.D. dissertation of Marvin Carmack.

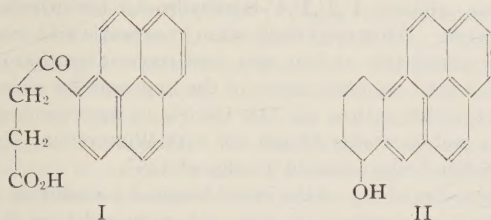
(2) Cook and Hewett, *J. Chem. Soc.*, 398 (1933).

(3) Fieser [*Am. J. Cancer*, **34**, 76 (1938)] has discussed the relative merits of the procedures that have been employed to prepare the hydrocarbon and its intermediates.

(4) Martin, *THIS JOURNAL*, **58**, 1438 (1936).

(5) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

when no acetic acid was employed in the reducing mixture as much as 35% of the compound was formed in small runs. Although the structure of the compound has not been established definitely, we consider the compound to be one of the two possible dilactones of the pinacol. This structure is indicated by the insolubility of the compound in cold aqueous alkali and its cleavage by hot concentrated alcoholic potassium hydroxide to the salts of the keto acid (I) and the corresponding hydroxy acid, γ -3-pyrenyl- γ -hydroxybutyric acid.



Another modification of the synthesis was introduced in the conversion of 4'-ketotetrahydrobenzpyrene to 3,4-benzpyrene. This has been accomplished by other investigators by heating the cyclic ketone with selenium preferably after preliminary reduction with sodium and alcohol²; by high-pressure catalytic reduction of the ketone to tetrahydrobenzpyrene followed by selenium dehydrogenation of the latter at 330° for thirty-six hours⁶; and by zinc dust distillation of the ketone. The latter method, suggested by Fieser and Fieser⁶ for small amounts, was employed on a fairly large scale by Vollmann and co-workers⁵ who considered this method to be the best one available. We have found that the conversion can be accomplished readily by first reducing the cyclic ketone to the corresponding secondary alcohol (II) by means of aluminum isopropoxide and then dehydrating and dehydrogenating the alcohol to 3,4-benzpyrene by means of palladium on charcoal. In a run in which all of the crude secondary alcohol was used in the second step without purification, the over-all conversion of the ketone to the hydrocarbon was 80%.

Experimental

β -3-Pyrenoylpropionic acid (I) was prepared by the method of Cook and Hewett² except that the Friedel-Crafts reaction was started at -5° and the mixture was stirred at -5 to 0° for only three hours after the addition of the pyrene (instead of keeping it at room temperature for twenty-four hours); then it was hydrolyzed and steam distilled. The sodium salt of the keto acid was precipi-

tated from its solution by means of sodium chloride,⁶ filtered, and washed with acetone. The free acid obtained from the sodium salt was purified further by boiling a solution of its ammonium salt with Norit and reprecipitating the acid. The yield of light yellow acid melting at 180–182° from 50 g. of pyrene was 64–68 g. Recrystallization from six volumes of a 3:1 mixture of xylene and acetic acid gave 61.5–63.5 g. (82–87%) of the acid; m. p. 181.5–182.5°. Vollmann and co-workers,⁵ using the Cook and Hewett procedure, obtained an 82% yield of recrystallized acid (m. p. 184°) and Fieser and Fieser⁶ reported a 90–94% yield of the sodium salt of the acid by their method in which sixteen hours were allowed for the reaction.

The methyl ester was formed when 5 g. of the keto acid was refluxed for one hour with 50 cc. of methanol saturated with hydrogen chloride. On cooling, a 95% yield of the ester separated as yellow rhombic crystals; m. p. 106–106.5°. Further purification by evaporative distillation at 0.01 mm. and recrystallization from methanol raised the melting point to 108–108.5°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{16}\text{O}_3$: C, 79.7; H, 5.1. Found: C, 79.2; H, 4.8.

Reduction of the Keto Acid.—After numerous trials in which the solvents, the relative proportions of the reagents and the time of heating were varied, the following procedure was adopted. Fifty g. of zinc (20-mesh) was cleaned by heating it with a solution of 5 cc. of 45% aqueous potassium hydroxide and 10 cc. of alcohol on a steam-bath for ten minutes; it was washed with water and with hydrochloric acid and then amalgamated with a solution of 2 g. of mercuric chloride in 40 cc. of water in acid solution. The amalgamated zinc, 30 cc. of concentrated hydrochloric acid, 30 cc. of acetic acid, 22.5 cc. of xylene and 7.5 cc. of chlorobenzene were placed in a 500-cc. round-bottomed flask in this order; 5 g. of recrystallized β -3-pyrenoylpropionic acid was then added carefully to the upper layer so that none of the solid dropped down on the zinc. After one-half hour of refluxing on a sand-bath the rather insoluble solid acid had disappeared. The mixture was refluxed for six hours; during this time two 10-cc. portions of concentrated hydrochloric acid were added. Usually some insoluble flocculent material (dilactone of the pinacol) appeared in the light transparent orange-red solution. The liquids were decanted from the zinc into a beaker (or alternately the mixture was allowed to cool in the flask until crystallization was complete when the crystals plus the zinc were filtered from the liquids); after about six hours of cooling the crystals of the product which had separated from the upper layer were filtered off, washed with water and a small amount of benzene and dried. The product (alone or with the zinc) was digested with a warm solution of 3 g. of sodium hydroxide in 150 cc. of water in order to separate the reduced acid from the insoluble colorless by-product (0.15–0.2 g.; m. p. 250–260°).

Acidification of the filtered alkaline solution yielded 3.7–3.78 g. of γ -3-pyrenylbutyric acid as a chalk white solid suitable for cyclization; m. p. 183.5–184.5°; with concentrated sulfuric acid it gave no trace of the red color given by the keto acid. From the xylene-chlorobenzene filtrate an additional 0.2–0.4 g. of satisfactory product was isolated (by warming the washed solution with dilute sodium hydroxide and recrystallizing the acid obtained from the alkaline solu-

(6) Fieser and Fieser, *THIS JOURNAL*, **57**, 782 (1935).

tion from acetone and benzene) which brought the yield to 80–84%. When the acid (15 g.) was purified by dissolving it in hot acetone, boiling the solution with Norit, filtering, evaporating and recrystallizing the residue from a 3:1 mixture of xylene and acetic acid, slightly colored platelets (12.7 g.) of the acid were obtained; m. p. 186–186.5°.

On runs in which 25 g. of the keto acid was reduced (six hours being allowed for the complete reaction) an average yield of 16.2 g. (68%) of product (m. p. 183–184°) was obtained from the crystals which precipitated from the organic layer in the reaction mixture. In one 25-g. run, only 2.5 g. of the keto acid was added to the mixture (250 g. of zinc and proportionate amounts of the other reagents) at the start; after twenty minutes of refluxing, a 2.5-g. portion of the keto acid was added through the top of the condenser followed immediately by 10 cc. of concentrated hydrochloric acid, which washed down most of the acid clinging to the sides of the condenser tube. This operation was repeated every twenty minutes until all of the keto acid had been added; the mixture was then refluxed for three hours longer. The yield of acid (m. p. 183–184°) including that isolated from the xylene–chlorobenzene filtrate was 18.2 g. (76%).

Chlorobenzene without the addition of xylene was used satisfactorily in some runs, but occasionally the layer settled down on the zinc and the yield and purity of the product was poor. The xylene served to keep the organic layer on top of the aqueous solution. A large excess of zinc appeared to be essential for satisfactory results, for the success of the reaction depended on reducing a given amount of keto acid as rapidly as possible. The recovered zinc may be used in another reduction after being cleansed with nitric acid.

A number of runs were made on the methyl ester of the keto acid using toluene as the upper solvent layer. In one run a mixture of 3 g. of the ester, 10 cc. of toluene, 20 cc. of concentrated hydrochloric acid, 20 cc. of acetic acid and 20 g. of amalgamated zinc was refluxed for thirty-eight hours; during this time four 5-cc. portions of hydrochloric acid were added. When the mixture was cooled, 2 g. (69%) of γ -3-pyrenylbutyric acid crystallized from the toluene layer.

The insoluble by-product (1 g.) from several runs was heated with a solution of 2 g. of potassium hydroxide in 5 cc. of absolute ethanol on a steam-bath. After one-half hour the clear solution was evaporated, the residue was dissolved in water and the solution was acidified. The product which consisted of a mixture of the keto acid and the corresponding hydroxy acid was heated in xylene for one hour in order to convert the hydroxy acid to its lactone. Digestion of the product obtained from the xylene with water, methanol and ammonium hydroxide dissolved the keto acid and left the lactone (0.29 g.). The γ -3-pyrenyl- γ -butyrolactone after evaporative distillation at 0.01 mm. and two recrystallizations from acetic acid melted at 176–176.5° alone and when mixed with a sample prepared as described by Cook and Hewett.²

4'-Hydroxy-1',2',3',4'-tetrahydro-3,4-benzpyrene (II).—The cyclic ketone 4'-ketotetrahydrobenzpyrene was prepared according to the excellent procedure of Fieser and Novello⁷ except that the reaction of the γ -3-pyrenylbutyric

acid (15 g., recrystallized) with phosphorus pentachloride and the cyclization of the acid chloride with stannic chloride were both carried out entirely at room temperature; one-half hour was allowed for the first step and eight hours for the second operation. In this manner 13.6 g. (96%) of light-yellow ketone, m. p. 168–171°, was obtained (reported,⁷ 85–95%; m. p. 163–165°). After recrystallization from benzene the m. p. was 170–173°; yield, 90%. From 12.5 g. of unrecrystallized γ -3-pyrenylbutyric acid (as obtained by acidification of a solution of its sodium salt), 9.15 g. of the ketone, m. p. 169–170.5° (171–172° on remelting) and 0.52 g. melting at 168–169.5° were obtained; total yield, 83%. This material was suitable for the next step.

Clemmensen reduction of a sample of the ketone using toluene yielded 1',2',3',4'-tetrahydro-3,4-benzpyrene in 60% yield. After recrystallization from acetic acid, evaporative distillation at 0.01 mm. and recrystallization from ethanol large colorless plates of the hydrocarbon were obtained which melted at 113–113.5°, in agreement with Fieser and co-workers^{6,8} and not with Winterstein, Vetter and Schön,⁹ who reported a value of 135°.

Reduction of 5 g. of the cyclic ketone by a solution (not clarified) of aluminum isopropoxide prepared from 2.5 g. of polished aluminum wire and 50 cc. of anhydrous isopropyl alcohol (one-half hour of refluxing followed by slow distillation through an upright air condenser of 21 cc. of distillate in the course of one and one-half hours) gave 78–90% yields of satisfactory secondary alcohol (II) in four runs but in others the yield and purity of the product were less satisfactory. Good results were obtained consistently with a stock solution of *M* vacuum-distilled aluminum isopropoxide in isopropyl alcohol (warmed just before use in order to dissolve all of the reagent). A mixture of 5 g. of the ketone and 100 cc. of the stock solution was refluxed for one-half hour and then distilled for one and one-half hours so that 45 cc. of distillate was collected; 45 cc. of anhydrous isopropyl alcohol was added and distillation was continued for thirty minutes when no test for acetone was obtained in the distillate.¹⁰

The solution was poured into 300 cc. of ice-cold 5% hydrochloric acid and the nearly colorless secondary alcohol was filtered and washed well with water and then with ammonium hydroxide. A benzene solution of the product was washed well with ammonium hydroxide and then with water and the solvent was removed at 25° under reduced pressure. The residue was dissolved in hot acetone, the solution was boiled with Norit and filtered, and absolute alcohol was added to the concentrated solution. The first crop of practically colorless needles (m. p. 140–141.5°) weighed 3.45 g. and the second crop (m. p. 139–141°) weighed 0.51 g.; total yield, 79%. A sample after recrystallization from benzene melted at 141.5–142°. It was somewhat difficult to obtain it entirely free from solvent. The alcohol gives an intense purple color with concentrated sulfuric acid.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9. Found C, 88.9; H, 6.2.

3,4-Benzpyrene.—Two grams of the cyclic ketone (prepared from unrecrystallized γ -3-pyrenylbutyric acid) was

(8) Fieser and Hershberg, *ibid.*, **60**, 1658 (1938).

(9) Winterstein, Vetter and Schön, *Ber.*, **68**, 1079 (1935).

(10) Lund, *ibid.*, **70**, 1520 (1937).

(7) Fieser and Novello, *THIS JOURNAL*, **62**, 1855 (1940).

reduced in the manner described and the crude alcohol (obtained by pouring the mixture into dilute hydrochloric acid, filtering and washing the solid with water and with ammonium hydroxide) without purification was heated with 0.2 g. of palladium-charcoal catalyst¹¹ in a large test-tube in an atmosphere of nitrogen at 310–320° for one and one-half hours. The material which had sublimed up along the sides of the tube was washed down with benzene, the solvent was evaporated and heating was continued for an additional two hours.

The product was separated from the catalyst by means of hot benzene, the solution was passed through a tower of alumina, the solvent was removed under reduced pressure and the 3,4-benzpyrene was recrystallized from benzene-methanol. The first two crops (1.55 g.) were combined and evaporatively distilled at 200–210° at 0.01 mm.; this left behind a trace of high-melting impurity. The product was dissolved in hot acetone, an equal volume of *n*-propyl alcohol was added and the solution was concentrated to incipient crystallization. On cooling, the 3,4-benzpyrene crystallized in large, thin sheets, which began to change to long, pale-yellow needles after a short time; the complete change required an hour or two. The first crop (1.43 g.) melted at 177.5–178.5° cor. (vac.) with slight previous

softening and remelted at 178–179°; the second crop (0.05 g.) melted at 175–176° cor.; total yield, 80%. A slightly higher yield of the hydrocarbon was obtained when recrystallized secondary alcohol was used.

A sample was purified further by making and recrystallizing the picrate, and passing the regenerated hydrocarbon through alumina; after recrystallization it melted at 178.6–179.8° cor. (vac.) with slight previous softening and remelted at 179–180° cor. (highest previously recorded value, 178.8–179.3° cor.¹²).

Summary

A procedure has been devised for reducing β -3-pyrenoylpropionic acid to γ -3-pyrenylbutyric acid by the Clemmensen method.

A new procedure for obtaining the carcinogenic hydrocarbon 3,4-benzpyrene from 4'-ketotetrahydrobenzpyrene in good yield is described. The cyclic ketone is reduced to the corresponding alcohol by means of aluminum isopropoxide and the alcohol is dehydrated and dehydrogenated to the hydrocarbon by palladium on charcoal.

(12) Fieser and Newman, *THIS JOURNAL*, **57**, 1602 (1935).

(11) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

Digitized by the Internet Archive
in 2026

[Reprinted from the Journal of the American Chemical Society, 63, 1685 (1941).]

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

4',5-Dimethylene-3,4-benzpyrene

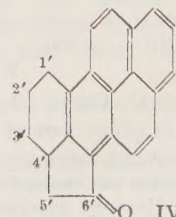
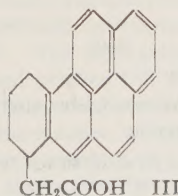
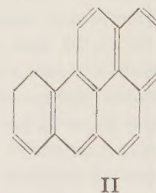
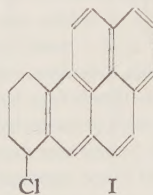
BY W. E. BACHMANN AND MARVIN CARMACK¹

The polycyclic hydrocarbon 4',5-dimethylene-3,4-benzpyrene (VI) is of particular interest in that it combines in one molecule the structural features of the two powerful carcinogens 3,4-benzpyrene and cholanthrene. We were interested in determining whether this compound would surpass its two prototypes in carcinogenic activity.

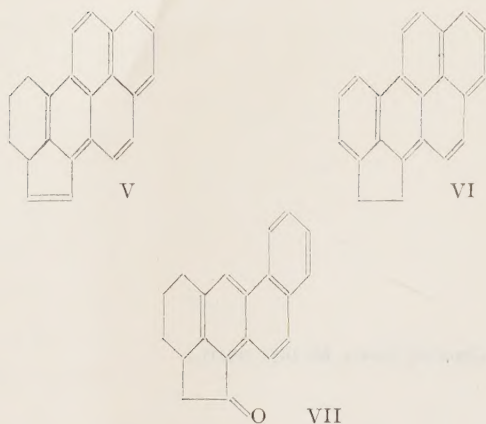
For its synthesis 4'-chlorotetrahydrobenzpyrene (I) was converted to 4'-tetrahydrobenzpyrenylacetic acid (III) through the malonic ester synthesis, and the acid was cyclized in practically quantitative yield to the ketone IV. A by-product in the malonic ester reaction was 1',2'-dihydro-3,4-benzpyrene (II), which was formed by elimination of the elements of hydrogen chloride from the chloride I. This hydrocarbon was prepared also by heating the chloride with pyridine. As was expected, the dihydro derivative was easily dehydrogenated by palladium to 3,4-benzpyrene.

After a number of unsuccessful trials to reduce the cyclic ketone (IV) by the Clemmensen method and by the Wolff-Kishner reaction, the following

method was evolved for obtaining the desired hydrocarbon. The ketone was reduced by means of aluminum isopropoxide and the resulting alcohol was dehydrated to a yellow hydrocarbon to which the structure V is assigned. When this hydrocarbon was heated with palladium on charcoal, it lost hydrogen and was converted to the beautifully crystalline orange colored 4',5-dimethylene-3,4-benzpyrene (VI).



(1) From the Ph.D. dissertation of Marvin Carmack.



During the treatment with palladium the double bond in the cyclopentene ring became reduced, a reaction for which there is precedent in the behavior during dehydrogenation of hydroaromatic compounds containing an exocyclic double bond.² Further confirmation of the correctness of the structure of the new hydrocarbon was obtained by carrying out the same series of reactions on 1-keto-tetrahydrocholanthrene (VII), whereby cholanthrene was obtained as the final product.

The curve for the absorption spectrum of 4',5-dimethylene-3,4-benzpyrene in ether is shown in Fig. 1 along with the curve for 3,4-benzpyrene in alcohol as determined by Mayneord and Roe.³

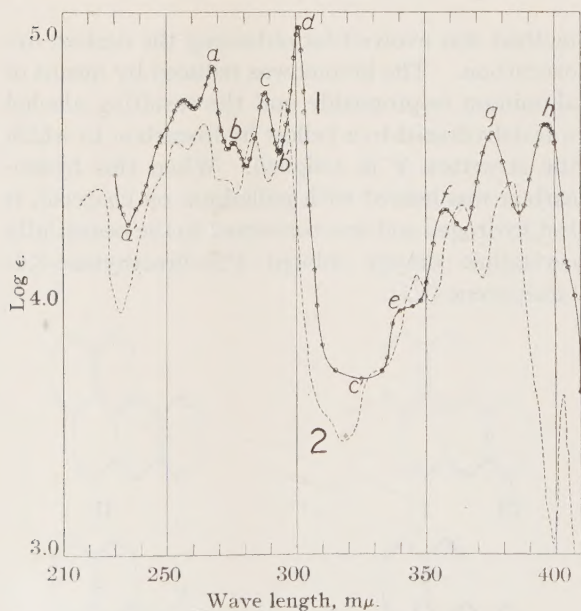


Fig. 1.—Curve 1, 4',5-dimethylene-3,4-benzpyrene; curve 2, 3,4-benzpyrene.

(2) Compare Bachmann and Wilds, *THIS JOURNAL*, **60**, 624 (1938); Bachmann and Chemerda, *ibid.*, **61**, 2358 (1939).

(3) Mayneord and Roe, *Proc. Roy. Soc. (London)*, **A152**, 299 (1935).

Following the procedure of Fieser and Hershberg,⁴ we have marked significant inflections in the curve by means of letters and have recorded the wave lengths of these points in Table I. The values for 3,4-benzpyrene are subject to a slight error since they were estimated from the published smooth curve of Mayneord and Roe.

TABLE I
COMPARISON OF ABSORPTION CHARACTERISTICS

Maxima and minima	4',5-Dimethylene-3,4-benzpyrene λ , m μ	3,4-Benzpyrene ⁵ λ , m μ
a'	235	232
a	267.5	264
b	275.5	272 ^a
c	288	284
b'	293.5	289
d	300.7	295.5
e'	325	319
e	342 ^a	331 ^a
f	357.5	346
g	376	364
h	396	384

^a Point of inflection.

From the curves and the table it is apparent that the absorption spectrum of 4',5-dimethylene-3,4-benzpyrene is very similar to that of 3,4-benzpyrene and that there is a general shift throughout toward the region of longer wave length. The shift in the near ultraviolet is more pronounced than that in the region of short wave length, being about 110–120 Å. for peaks e, f, g, and h, and only 35–50 Å. for peaks a, b, c and d. Although the values of log ϵ appeared to be slightly higher than for 3,4-benzpyrene, the difference may not be significant; one reason for this is the fact that the measurements were made in different solvents.

This bathochromic shift of the spectrum of 4',5-dimethylene-3,4-benzpyrene is of interest in connection with the tests for carcinogenic activity which are being carried out on the hydrocarbon. Jones⁵ has observed that "some correlation can be traced between the carcinogenic activity and the bathochromic shift of band D" (of which d is the maximum) of various derivatives of 1,2-benzanthracene. Thus, the d peak of the carcinogen cholanthrene (2950 Å.) is shifted 80 Å. to the long wave region with reference to the corresponding band of 1,2-benzanthracene (2870 Å.), and in 3,4-benzpyrene there is a shift of 85 Å., although this hydrocarbon was included in the comparison with

(4) Fieser and Hershberg, *THIS JOURNAL*, **60**, 940 (1938).

(5) Jones, *ibid.*, **62**, 148 (1940).

some reservation since its spectrum differs from that of 1,2-benzanthracene in the long wave part. In 4',5-dimethylene-3,4-benzpyrene the peak d is located at 3007 Å., corresponding to a shift of 137 Å., which is greater than the shift in the spectrum of cholanthrene and of 3,4-benzpyrene. The hydrocarbon 1',2'-dihydro-3,4-benzpyrene is also being tested for carcinogenic activity.

Experimental

4'-Chloro-1',2',3',4'-tetrahydro-3,4-benzpyrene (I).—Dry hydrogen chloride was passed through a suspension of 7 g. of 4'-hydroxy-1',2',3',4'-tetrahydro-3,4-benzpyrene⁶ in 35 cc. of dry benzene at room temperature for thirty-five minutes. The needle-like crystals of the alcohol change rapidly to fine rhombic crystals of the chloride. After the addition of 10 cc. of petroleum ether, the mixture was cooled and the crystals were filtered off; yield, 7.04 g. (94%); m. p. 145°, dec., when placed in a bath at 140°. The product so obtained was used immediately in the next step without further purification since the chloride decomposes readily. A sample after two recrystallizations from benzene formed pale-yellow rhombic crystals; m. p. 150° (cor.), dec.

Anal. Calcd. for $C_{20}H_{15}Cl$: C, 82.6; H, 5.2. Found: C, 82.6; H, 5.5.

4'-(1',2',3',4'-Tetrahydro-3,4-benzpyrenyl)-acetic Acid (III).—To the sodio-malonic ester prepared from 2 g. of powdered sodium and 17.5 cc. of malonic ester in 50 cc. of benzene was added 7.7 g. of the aforementioned chloride and 25 cc. of benzene. The mixture was warmed gradually with continuous swirling and then refluxed on a steam-bath for fourteen hours. The benzene was evaporated in a current of air and the ester was hydrolyzed by heating it with 40 cc. of 40% aqueous potassium hydroxide on a steam-bath for two hours. Water was added to dissolve the crystalline salt which had separated, the solution was filtered from a small amount (0.2–0.3 g.) of crystalline 1',2'-dihydro-3,4-benzpyrene (II), and the filtrate was poured into dilute hydrochloric acid. The practically colorless substituted malonic acid weighed 8.8 g. (93%).

Five grams of the product was decarboxylated at 190–200° and the tetrahydrobenzpyrenylacetic acid was recrystallized from a mixture of benzene and acetic acid, from which it separated as light tan crystals suitable for the next step; yield, 3.86 g. (88%); m. p. 187.5–188.5°. After evaporative distillation at 0.01 mm. and recrystallization from acetic acid a sample of the acid formed colorless needles which exhibited two melting points. When heated slowly it melted at 188–193°; when placed in a bath at 189°, it melted completely, the melt solidified and remelted at 194–195°.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.0; H, 5.8. Found: C, 83.9; H, 5.7.

1',2'-Dihydro-3,4-benzpyrene (II).—A mixture of 0.46 g. of 4'-chlorotetrahydrobenzpyrene (I) and 5 cc. of pyridine was refluxed for fifteen minutes and then poured into dilute hydrochloric acid and benzene. From the benzene layer 0.17 g. of crystalline dihydrobenzpyrene was isolated.

After evaporative distillation at 0.5 mm. and three recrystallizations from ether–alcohol, it formed light-yellow platelets; m. p. 149.5–150°. The warm acid solution deposited nearly colorless crystals (0.26 g.) of what were probably the pyridinium salt of the chloride. When heated at 250° the salt decomposed and from the product practically pure dihydrobenzpyrene was obtained by evaporative distillation under reduced pressure.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.4; H, 5.6. Found: C, 94.2; H, 5.6.

The picrate crystallized from benzene in brownish-red prisms; m. p. 170–180°, dec.

Anal. Calcd. for $C_{20}H_{11} \cdot C_6H_3N_3O_7$: N, 8.7. Found: N, 8.8.

A mixture of 0.2 g. of dihydrobenzpyrene and 20 mg. of palladium-charcoal catalyst was heated in a nitrogen atmosphere at 320° for one hour. From the mixture was obtained 0.2 g. of 3,4-benzpyrene melting at 172.5–174.5°. By recrystallization from benzene-methanol the hydrocarbon was obtained as pale yellow needles; m. p. 176–176.5°.

6'-Keto-4',5-dimethylene-1',2',3',4'-tetrahydro-3,4-benzpyrene (IV).—A mixture of 2 g. of the tetrahydrobenzpyrenylacetic acid (III) and 1.44 g. of finely powdered phosphorus pentachloride in 40 cc. of benzene was allowed to stand at room temperature for forty minutes with frequent swirling. Then 1 cc. of anhydrous stannic chloride was added dropwise with swirling; a deep-red complex precipitated immediately. After forty-five minutes at room temperature, the complex was hydrolyzed and worked up in the usual manner. The benzene solution after being washed was combined with a similar solution from 1 g. of the acid; from the combined solutions 2.77 g. (98%) of the cyclic ketone was isolated in the form of golden-yellow prisms; m. p. 192–193° (vac.). The melting point was not raised when a sample was sublimed at 0.01 mm. and then recrystallized from benzene. In an open tube the compound darkened and melted at a slightly lower temperature. The ketone gives an orange-red color (green fluorescence) with concentrated sulfuric acid. Alcoholic solutions of the ketone show an intense blue fluorescence.

Anal. Calcd. for $C_{22}H_{16}O$: C, 89.2; H, 5.4. Found: C, 88.9; H, 5.4.

4',5-Dimethylene-3,4-benzpyrene (VI).—The ketone (2 g.) was added to a solution of aluminum isopropoxide prepared from 1.35 g. of aluminum wire and 50 cc. of anhydrous isopropyl alcohol. The mixture was alternately refluxed and distilled slowly through an upright column for approximately four hours; an additional 30 cc. of isopropyl alcohol was added during this time. When no further test for acetone could be detected in the distillate by means of 2,4-dinitrophenylhydrazine reagent, the mixture was cooled and hydrolyzed with ice and dilute hydrochloric acid. The light-yellow crystalline solid which was obtained weighed 1.97 g.

The product was dehydrated in three portions in the following manner. Each portion was heated rapidly to 180° under a pressure of 1 mm., whereupon water was evolved for approximately ten minutes. The pressure was then reduced to 0.01 mm. and the temperature raised to 320°, whereupon a yellow crystalline solid collected on the cool

part of the sublimation tube; yield, 1.23 g. (65%); m. p. 203–208°. In one run 0.6 g. (78%) of sublimed product was obtained from 0.81 g. of the cyclic ketone. A sample of the hydrocarbon (V) crystallized from benzene in yellow rhombic plates; m. p. 209–213°. It dissolves slowly in concentrated sulfuric acid to give an emerald green solution.

Anal. Calcd. for $C_{22}H_{16}$: C, 94.2; H, 5.7. Found: C, 93.7; H, 5.7.

The picrate crystallized from benzene in dark-red needles; m. p. 177.5–178°.

Anal. Calcd. for $C_{22}H_{16} \cdot C_6H_3N_3O_7$: N, 8.3. Found: N, 8.3.

The unrecrystallized hydrocarbon (1.23 g.; m. p. 203–208°) and 0.2 g. of palladium-charcoal catalyst⁷ were heated in a nitrogen atmosphere at 310–330°. After twenty minutes the material which had sublimed up on the sides of the tube was washed down with a little benzene, the benzene was evaporated and the heating continued for ten minutes. The product was then sublimed directly from the catalyst at 0.01 mm.; the bright orange sublimate weighed 0.97 g. and melted at 240–246.5° (vac.). A solution of 1.2 g. of such sublimed product in benzene was passed through a short tower of alumina and the solution was concentrated under reduced pressure; addition of a little petroleum ether caused the 4',5-dimethylene-3,4-benzpyrene to separate as bright orange platelets; yield, 0.78 g.; m. p. 251–252° (255–256° cor.) in an evacuated tube; the melting point in air is somewhat lower because of oxidation. From the filtrate an additional 0.29 g. of practically pure hydrocarbon was isolated. The hydrocarbon is very slightly soluble in cold alcohol and ether, slightly soluble in cold benzene and only moderately soluble in boiling benzene. It gives a violet color with concentrated sulfuric acid; in a few minutes the color changes to a beautiful magenta (yellow-orange fluorescence).

Anal. Calcd. for $C_{22}H_{14}$: C, 94.9; H, 5.1. Found: C, 94.8, 95.23; H, 4.9, 5.0.

(7) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

The picrate crystallized from benzene in almost black needles; m. p. 177–177.5°.

Anal. Calcd. for $C_{22}H_{14} \cdot C_6H_3N_3O_7$: N, 8.3. Found: N, 8.4.

Conversion of 1-Ketotetrahydrocholanthrene (VII) to Cholanthrene.—One-half gram of the ketone⁸ was reduced by aluminum isopropoxide in the manner described. The crude 1-hydroxytetrahydrocholanthrene was recrystallized from benzene, from which it separated in fine colorless rhombic platelets and needles. The first crop weighed 0.32 g. and melted at 146.5–147.5°; this was suitable for the next step. A sample after another recrystallization melted at 150–150.5°.

Anal. Calcd. for $C_{26}H_{18}O$: C, 87.6; H, 6.6. Found: C, 87.6; H, 6.8.

Dehydration of 100 mg. of the secondary alcohol by heating it gradually to 240° at 5 mm. and after cessation of frothing evaporatively distilling at 0.05 mm. gave 80 mg. of product melting at 136–137°. When this was dehydrogenated with palladium on charcoal in the manner described, there was obtained 51 mg. of practically pure cholanthrene.

Summary

The polycyclic hydrocarbon 4',5-dimethylene-3,4-benzpyrene which possesses the basic structures of both cholanthrene and 3,4-benzpyrene has been synthesized from 4'-ketotetrahydro-3,4-benzpyrene and its absorption spectrum has been measured.

The preparation of 1',2'-dihydro-3,4-benzpyrene is described. The two new polycyclic hydrocarbons are being tested for carcinogenic activity.

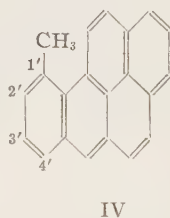
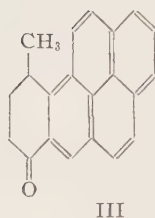
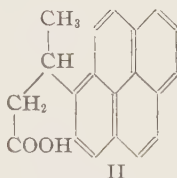
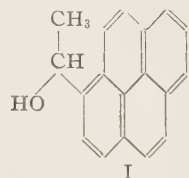
(8) Bachmann, *J. Org. Chem.*, **3**, 434 (1938).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

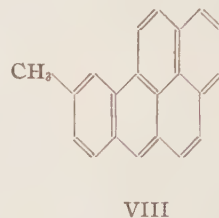
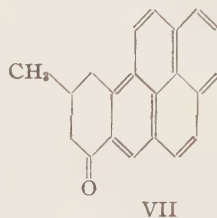
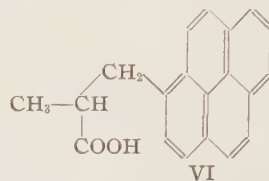
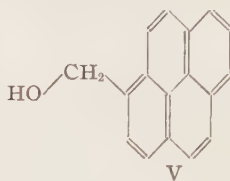
Methyl Derivatives of 3,4-Benzpyrene. The Willgerodt Reaction on Some 3-Acylpyrenes

BY W. E. BACHMANN AND MARVIN CARMACK¹

For the synthesis of 1'-methyl-3,4-benzpyrene (IV), a new methyl derivative of the carcinogen 3,4-benzpyrene, the readily available 3-acetylpyrene was reduced to methyl-3-pyrenylcarbinol (I) by means of aluminum isopropoxide, the carbinol was converted to its bromide and the latter was condensed with sodio-malonic ester to yield β -3-pyrenylbutyric acid (II). The side chain was lengthened by one methylene group and the resulting γ -3-pyrenylvaleric acid was cyclized to 1'-methyl-4'-ketotetrahydro-3,4-benzpyrene (III). The ketone was reduced to the corresponding alcohol and the latter was dehydrated and dehydrogenated to 1'-methyl-3,4-benzpyrene by palladium on charcoal at 300–320°.



properties of our compound agreed with those of the hydrocarbon which Fieser and Hershberg² obtained from *p*-toluylperinaphthane through the Scholl reaction and which they regarded as 2'-methyl-3,4-benzpyrene.



Winterstein, Vetter and Schön³ prepared a methyl-3,4-benzpyrene from the keto acid obtained by interaction of pyrene and methylsuccinic anhydride, but they were uncertain whether their compound was the 2'- or 3'-methyl isomer, for they were unable to decide how the unsymmetrical anhydride oriented itself when it reacted with the pyrene. We have now proved that the keto acid which is formed possesses the structure XI; the anhydride reacts with pyrene in the 3-position in such a manner that the methyl group is farthest away from the hydrocarbon residue, in harmony with the reaction of the anhydride with other hydrocarbons. Fieser and Hershberg² considered that the hydrocarbon which they obtained from both *o*- and *m*-toluylperinaphthane and which agreed fairly well in melting point with the hydrocarbon of Winterstein, Vetter and Schön was 3'-methyl-3,4-benzpyrene. In the present investigation, 3'-methyl-3,4-benzpyrene has been synthesized by a method which leaves no doubt about the structure, and it has been shown that this is the compound which was obtained by Winterstein, Vetter and Schön. The properties of the hydrocarbon and its derivatives prepared by Fieser and Hershberg agree with the proper-

In the synthesis of 2'-methyl-3,4-benzpyrene, 3-pyrenealdehyde was reduced to 3-pyrenylcarbinol (V) catalytically and also by means of aluminum isopropoxide. The carbinol was converted to its chloride, which was condensed with sodio-malonic ester. The substituted malonic ester was hydrolyzed to the free dicarboxylic acid which was purified and then converted to its dimethyl ester. The latter was methylated and the product was hydrolyzed and decarboxylated to yield β -3-pyrenylisobutyric acid (VI). The side chain was lengthened by one methylene group and the resulting acid was cyclized through its acid chloride to 2'-methyl-4'-ketotetrahydro-3,4-benzpyrene (VII), which was converted to 2'-methyl-3,4-benzpyrene (VIII) by the procedure employed for the 1'-methyl isomer. The

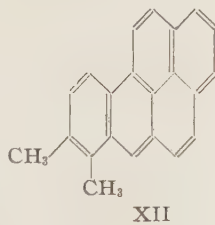
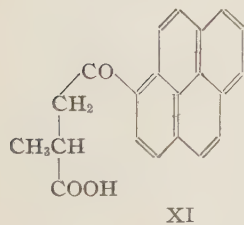
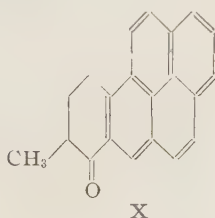
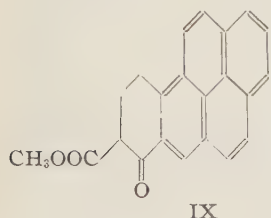
(1) From the Ph.D. dissertation of Marvin Carmack.

(2) Fieser and Hershberg, *THIS JOURNAL*, **60**, 1658 (1938).(3) Winterstein, Vetter and Schön, *Ber.*, **68**, 1079 (1935).

ties of 3'-methyl-3,4-benzpyrene and its derivatives prepared by us.

In our synthesis, 4'-ketotetrahydrobenzpyrene was condensed with dimethyl oxalate and the resulting glyoxalate was decarbonylated by heating it with powdered glass.⁴ The keto ester (IX), which was formed, was methylated and the product was hydrolyzed and decarboxylated to 3'-methyl-4'-ketotetrahydrobenzpyrene (X). By reduction of the ketone to the alcohol by means of aluminum isopropoxide and heating the alcohol with palladium on charcoal, 3'-methyl-3,4-benzpyrene was obtained in good yield.

The hydrocarbon 3',4'-dimethyl-3,4-benzpyrene (XII) was also synthesized. This was accomplished by treating the ketone (X) with methylmagnesium iodide and dehydrating and dehydrogenating the resulting carbinol to the hydrocarbon by means of palladium.



Willgerodt Reaction on Some 3-Acylpyrenes.

—This reaction was applied to a number of 3-acylpyrenes, which were prepared readily from pyrene and the acid anhydride through the Friedel-Crafts reaction. The ketones were heated with ammonium polysulfide in dioxane according to the procedure of Fieser and Kilmer⁵ in order to convert them to the amide of the acid with the same number of carbon atoms. On small scale runs, 3-acetylpyrene gave practically pure 3-pyrenylacetamide in yields as high as 92%. Hydrolysis of the product yielded 3-pyrenylacetic acid, whose structure was verified by its synthesis from 3-pyrenylcarbinol (V). The over-all yield of the acid from pyrene was 73%. This acid was obtained by Vollmann and co-workers⁶ in 10%

yield by the prolonged action of chloroacetic acid on pyrene.

From 3-propionylpyrene a 67% yield of β -3-pyrenylpropionic acid was obtained through the amide. The structure of this acid was proved by its preparation from 3-pyrenylcarbinol through the malonic ester synthesis. Similarly, a 46% yield of γ -3-pyrenylbutyric acid was obtained from 3-*n*-butyrylpyrene through the amide produced in the Willgerodt reaction. We were not able to obtain any amide from 3-pyrenyl isopropyl ketone or from 3-pyrenyl isobutyl ketone, which contain branched alkyl groups. It is of interest that Fieser and Kilmer obtained only a 1.8% yield of amide from phenyl isobutyl ketone.

Experimental

Methyl-3-pyrenylcarbinol (I).—3-Acetylpyrene (20 g.) was reduced by a solution of aluminum isopropoxide prepared from 5 g. of aluminum wire and 125 cc. of anhydrous isopropyl alcohol. The mixture was hydrolyzed with ice-cold dilute sulfuric acid and the product was filtered, washed thoroughly with water and dried. A solution of the compound in acetone was boiled with Norit, the solution was filtered and evaporated and the residue was recrystallized from benzene, yielding 17.4 g. of pale yellow crystals suitable for the next step; m. p. 109–110°. A sample after several recrystallizations from benzene formed clusters of colorless prisms; m. p. 112–112.5°.

Anal. Calcd. for $C_{18}H_{14}O$: C, 87.8; H, 5.7. Found: C, 87.8; H, 5.7.

β -3-Pyrenylbutyric Acid (II).—The aforementioned carbinol (6.25 g.) in 25 cc. of pure benzene was treated with 1.9 cc. of phosphorus tribromide. Enough benzene (35 cc.) was added to dissolve all of the solid and the mixture was allowed to remain at room temperature for one hour. The solution was washed three times with 5% sodium bicarbonate solution, then with water and dried with magnesium sulfate. From the solution 7.6 g. (96%) of 1-bromo-1-(3-pyrenyl)-ethane (m. p. 108° dec.) was obtained, which was used immediately in the next step. In one run, the crude carbinol obtained from 11.8 g. of 3-acetylpyrene yielded 14.4 g. (96% based on the ketone) of the bromide (m. p. 105–106° dec.) suitable for the next step.

Finely powdered sodium (2.9 g.) was refluxed with 26 cc. of diethyl malonate in 100 cc. of benzene for three hours, and to the cooled suspension was added 12 g. of the crude bromide. After the mixture had been refluxed for thirteen hours on a steam-bath, the benzene was removed by distillation and the ester was hydrolyzed by heating it with 35 cc. of 40% potassium hydroxide solution for four hours on a sand-bath. After extraction with benzene, the solution was acidified and the substituted malonic acid was collected; yield, 12 g. (93%) of a pale tan colored solid. The latter was heated at 180–190° for twenty-five minutes and the product was recrystallized from chlorobenzene (25 cc.), yielding 9.08 g. of crystalline acid suitable for the next step. A sample after evaporative distillation at 0.01

(4) Bachmann, Cole and Wilds, *THIS JOURNAL*, **62**, 825 (1940).

(5) Fieser and Kilmer, *ibid.*, **62**, 1354 (1940).

(6) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

mm. and recrystallization from benzene-acetic acid formed colorless rhombic crystals; m. p. 177–178°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.0; H, 5.5.

γ -3-Pyrenylvaleric Acid.—The acid chloride was prepared in a small filter flask from 2 g. of the aforementioned acid, 0.8 cc. of pure thionyl chloride, 10 cc. of anhydrous ether and a drop of pyridine. After two hours at room temperature (frequent swirling), the ether and excess of thionyl chloride were removed under reduced pressure, a few cc. of dry benzene was added and the solvent again removed, finally at 40–50° at 0.5 mm. A solution of the acid chloride in 10 cc. of benzene was added dropwise from the side-arm of the flask to an ice-cold solution of diazomethane prepared from 4 g. of nitrosomethylurea in 40 cc. of ether. After ten minutes the diazoketone began to separate in lustrous pale tan platelets. After three hours at 5°, the ether was removed under reduced pressure and the crystalline residue was digested with cold methanol in order to remove oily impurities and filtered; yield, 1.92 g. (88%); m. p. 116–118° dec.

A mixture of 0.5 g. of silver oxide (Schuchardt) and 40 cc. of reagent methanol was refluxed until a silver mirror was visible on the bottom of the flask (fifteen minutes). The diazoketone was added and the mixture was refluxed for three hours, treated with Norit, filtered and evaporated in a current of air. The residual ester was refluxed with *N* sodium hydroxide (15 cc.) and a little methanol for one hour, and the clarified solution was acidified, yielding 1.82 g. of γ -3-pyrenylvaleric acid (m. p. 117–121°), which was suitable for the next step. A sample after recrystallization from chlorobenzene, evaporative distillation under reduced pressure and recrystallization from benzene-acetic acid formed fine colorless rhombic platelets; m. p. 135.5–136.5°.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.4; H, 6.0. Found: C, 83.2; H, 5.9.

1'-Methyl-4'-keto-1',2',3',4'-tetrahydro-3,4-benzpyrene (III).—Crude γ -3-pyrenylvaleric acid (1.2 g.; m. p. 117–121°) and 1.2 g. of finely divided phosphorus pentachloride were suspended in 20 cc. of dry benzene; after one-half hour, 1.3 cc. of anhydrous stannic chloride was added. After four hours at room temperature, the deeply colored complex was hydrolyzed with ice and hydrochloric acid. From the benzene solution, after thorough washing with acid and then with dilute alkali, 0.83 g. of the cyclic ketone was obtained as yellow needles; m. p. 154–160°. A sample after recrystallization from benzene-petroleum ether melted at 162–163°.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.7; H, 5.7. Found: C, 88.5; H, 5.6.

1'-Methyl-3,4-benzpyrene (IV).—One gram of the cyclic ketone was reduced by means of a clarified solution of aluminum isopropoxide prepared from 0.5 g. of aluminum and 50 cc. of isopropyl alcohol and the product obtained on hydrolysis with cold, dilute sulfuric acid was filtered and washed thoroughly with sodium bicarbonate solution and with water. On recrystallization from benzene-acetone a first crop of 0.51 g. of practically colorless platelets was obtained; the filtrate contained an amount which brought the yield to 91%. After another recrystallization

the 1'-methyl-4'-hydroxy-1',2',3',4'-tetrahydro-3,4-benzpyrene melted at 184–185°.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.1; H, 6.3. Found: C, 87.9; H, 6.3.

The unrecrystallized alcohol obtained from 0.73 g. of the cyclic ketone was heated with 0.1 g. of palladium-charcoal catalyst⁷ in a nitrogen atmosphere at 300–320° for twenty minutes. The material which had sublimed up on the sides of the tube was washed down with a little benzene, the benzene was evaporated and the heating was resumed for an additional ten minutes. After evaporative distillation at 220° and 0.01 mm. directly from the catalyst and recrystallization from benzene-methanol, the 1'-methyl-3,4-benzpyrene was obtained in glistening yellow platelets; yield, 0.34 g. (50%); m. p. 190–190.8° (vac.).

Anal. Calcd. for $C_{21}H_{14}$: C, 94.7; H, 5.3. Found: C, 94.5; H, 5.5.

The **picrate** prepared in benzene-petroleum ether crystallized in dark red-brown needles; m. p. 186–186.5°.

Anal. Calcd. for $C_{21}H_{14} \cdot C_6H_3N_3O_7$: N, 8.5. Found: N, 8.5.

The **trinitrobenzene complex**, prepared in benzene, crystallized in brilliant red needles; m. p. 208.5–209°.

Anal. Calcd. for $C_{21}H_{14} \cdot C_6H_3N_3O_6$: N, 8.8. Found: N, 8.6.

3-Pyrenylcarbinol (V).—Fifteen grams of 3-pyrenealdehyde, prepared from pyrene and methylformanilide,⁶ was hydrogenated in 200 cc. of absolute alcohol with the aid of 0.3 g. of Adams catalyst and a solution of 50 mg. of ferrous sulfate in 3 cc. of water as a promoter; absorption of hydrogen was complete in one to one and a half hours. The clear solution was filtered from the catalyst and chilled; after several hours 8.8 g. of the carbinol was filtered off; m. p. 121.5–122.5°. A second crop (3.5 g.; m. p. 121–122°) brought the yield to 81%. A sample of the carbinol after evaporative distillation at 0.01 mm. and recrystallization from benzene formed pale yellow rhombic crystals; m. p. 123–124°.

Anal. Calcd. for $C_{17}H_{12}O$: C, 87.9; H, 5.2. Found: C, 87.4; H, 5.1.

The carbinol was obtained in 54% yield by reduction of the aldehyde by means of aluminum isopropoxide.

α -Methyl- β -3-pyrenylpropionic Acid (VI).—Powdered 3-pyrenylcarbinol (2.3 g.) in 20 cc. of dry benzene was treated with 0.4 cc. of phosphorus trichloride. After one hour the clear filtered solution was washed with 5% sodium bicarbonate solution and with water and dried over magnesium sulfate. Removal of the benzene left 2.2 g. (89%) of cream-colored crystals of 3-chloromethylpyrene (m. p. 144–145°) suitable for the next step.

Eight grams of the chloride was added to a cooled suspension of sodio-malonic ester which had been prepared from 15.4 cc. of diethyl malonate and 1.5 g. of finely divided sodium in 100 cc. of dry benzene. The mixture was warmed slowly to boiling on a steam-bath with constant swirling and then heated for ten hours. After removal of the benzene in a current of air, the residual ester was hydrolyzed by heating it with 50 cc. of 40% aqueous potassium hydroxide on a steam-bath for one hour. After

(7) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

being warmed with 100 cc. of water to dissolve the salts which had precipitated, the clarified solution was acidified, whereupon 8.7 g. of nearly colorless substituted malonic acid was obtained. A mixture of 6.5 g. of the acid and 100 cc. of methanol which had been saturated cold with hydrogen chloride was refluxed for two hours. From the filtered solution 3.4 g. of **dimethyl- β -3-pyrenylisosuccinate** (m. p. 111–111.5°) crystallized in colorless needles; re-treatment of the filtrate with hydrogen chloride followed by refluxing yielded an additional 1.2 g. of satisfactory material. After evaporative distillation at 0.01 mm. and recrystallization from methanol a sample of the ester melted at 112–112.5°.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.3; H, 5.2. Found: C, 76.1; H, 5.1.

Four grams of the ester was added to a solution of sodium methoxide prepared from 1.46 g. of sodium and 50 cc. of methanol. After a short period of refluxing, the mixture was cooled to room temperature and treated with 4 cc. of methyl iodide; after two hours another 1 cc. of methyl iodide was added and the mixture was refluxed for two hours. After removal of the methanol, the product was taken up in benzene and water, the benzene solution was filtered from a small amount of high-melting by-product and then washed with dilute alkali and with water. Removal of the solvent yielded 3.47 g. (83%) of crystalline **dimethyl α -methyl- β -3-pyrenylisosuccinate**; m. p. 131–133°. A sample after evaporative distillation at 0.01 mm. and recrystallization from methanol–acetone was obtained in faintly yellow rhombic plates; m. p. 136.5–137.5°.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 76.6; H, 5.6. Found: C, 76.2; H, 5.6.

A mixture of 3.47 g. of the unrecrystallized ester and 35 cc. of 40% aqueous potassium hydroxide was refluxed for twenty minutes on a sand-bath; then 35 cc. of water was added to dissolve the salts which had precipitated and refluxing was continued for one hour. The dicarboxylic acid which was obtained on acidification of the solution was heated at 190–200° for one-half hour and the product was dissolved in hot acetone; from the solution 2.74 g. (98%) of satisfactory **α -methyl- β -3-pyrenylpropionic acid** was obtained; m. p. 170–173°. After evaporative distillation at 200° and 0.01 mm. and recrystallization from chlorobenzene a sample formed colorless rhombic crystals; m. p. 173–174°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.1; H, 5.8.

2'-Methyl-4'-keto-1',2',3',4'-tetrahydro-3,4-benzopyrene (VII).—The acid chloride was prepared from 1 g. of the aforementioned acid and converted to the diazoketone by the procedure described for the preparation of γ -3-pyrenylvaleric acid; m. p. 110–111° dec.; yield, 1.08 g. of fine pale tan crystals. The diazoketone was heated with 40 cc. of methanol and 0.15 g. of silver oxide in a water-bath for twenty minutes; a further 0.15 g. of silver oxide was added and refluxing was continued for one and one-half hours. The ester obtained by evaporation of the filtered solution was heated with 1 cc. of aqueous 40% potassium hydroxide and 10 cc. of water for three hours, the diluted solution was clarified with Filter-Cel, cooled and acidified. The crude **β -methyl- γ -3-pyrenylbutyric acid** (0.97 g.;

m. p. 125–135°) which precipitated was treated with 0.97 g. of phosphorus pentachloride in 15 cc. of dry benzene and the resulting mixture was treated with 1.1 cc. of stannic chloride at room temperature in the manner described. After forty-five minutes the mixture was hydrolyzed. From the washed and dried benzene solution 0.89 g. (90% over-all yield based on VII) of the cyclic ketone was obtained as yellow needles; m. p. 176.5–177.5°. After evaporative distillation at 0.01 mm. and recrystallization from benzene–methanol, a sample formed light yellow plates; m. p. 178–179° (vac.). From benzene–petroleum ether it crystallized in fine needles which then changed to plates.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.7; H, 5.7. Found: C, 88.5; H, 6.0.

2'-Methyl-3,4-benzopyrene (VIII).—One-half gram of the aforementioned ketone was reduced by a clarified solution of aluminum isopropoxide prepared from 0.27 g. of aluminum and 20 cc. of anhydrous isopropyl alcohol and the crude alcohol (0.52 g.; m. p. 160–170°) was heated with palladium–charcoal in the manner described. The hydrocarbon was evaporatively distilled directly from the catalyst at 175° and 0.01 mm. and the product was recrystallized twice from benzene–methanol, whereby it was obtained in fine yellow needles; yield, 0.15 g. (32%, based on the ketone). It melted at 139–140° cor. (vac.), when heated slowly (reported,² 138–139°, cor.); the solidified melt remelted at 140–140.4°, cor. (reported, 140–140.2°). The **picrate** formed fine, chocolate-brown crystals in benzene–petroleum ether which melted at 184–184.5° cor. (reported,² 184–185°, cor.) and the **trinitrobenzene complex** formed bright red rhombs in benzene–petroleum ether which melted at 212.5–213°, cor. (reported,² 211.5–212°, cor.).

3'-Methyl-4'-keto-1',2',3',4'-tetrahydro-3,4-benzopyrene (X). (a) **From XI.**— β -3-Pyrenylisobutyric acid was prepared from pyrene and methylsuccinic anhydride according to the procedure of Winterstein, Vetter and Schön.³ Its **methyl ester**, prepared by means of methanolic hydrogen chloride, after evaporative distillation at 0.01 mm., crystallized from methanol in light yellow platelets; m. p. 105–105.5°.

Anal. Calcd. for $C_{22}H_{18}O_3$: C, 80.0; H, 5.5. Found: C, 80.3; H, 5.4.

Clemmensen reduction of the keto acid and of its methyl ester yielded **α -methyl- γ -3-pyrenylbutyric acid (XI)**, which crystallized from benzene–acetic acid in bright yellow crystals; m. p. 173–174.5°; yield, 32%. Winterstein, Vetter and Schön obtained an 80% yield of this acid (m. p. 176°, cor.) by reduction of the keto acid by zinc and alkali. The acid (1.89 g.) was converted to its acid chloride by means of 1.5 g. of phosphorus pentachloride in 40 cc. of benzene and the mixture treated with anhydrous stannic chloride in the manner described for the preparation of III. The first crop of crystals from benzene–ethanol weighed 1.31 g. (74%); m. p. 177.3–178° (vac.). Further recrystallization of a sample of the ketone raised the melting point to 178–178.5° (vac.). Winterstein, Vetter and Schön obtained an 80% yield of the ketone by heating the acid with stannic chloride; their purified product melted at 176–177°, cor. A mixture of this ketone with its 2'-methyl isomer (m. p. 178–179°) melted to 150–165°.

(b) From 4'-ketotetrahydro-3,4-benzpyrene.—One-half gram of the ketone⁸ was condensed with 0.3 g. of dimethyl oxalate in 15 cc. of dry benzene by means of dry sodium methoxide (prepared from 0.07 g. of sodium) at room temperature in a nitrogen atmosphere. After one hour, water was added to the mixture, the benzene layer was discarded and the aqueous solution was acidified, whereupon methyl 4'-ketotetrahydro-3,4-benzpyrene-3'-glyoxalate was precipitated as a yellow crystalline powder; weight, 0.63 g. A sample crystallized from dioxane in golden yellow leaflets and orange-yellow rhombs; m. p. 172–174°, dec., in a Pyrex tube. The m. p. was variable and was from five to ten degrees lower in soft glass capillary tubes.

Anal. Calcd. for $C_{22}H_{16}O_4$: C, 77.5; H, 4.5. Found: C, 76.8; H, 4.6.

Recrystallized glyoxalate (1 g.) was heated with 0.5 g. of powdered soft glass at 180–190° for fifteen minutes. The product was extracted with hot acetone, and the solution was heated with Norit, filtered and evaporated, yielding 0.83 g. of nearly pure 3'-carbomethoxy-4'-ketotetrahydrobenzpyrene (IX). From acetone-dioxane it crystallized in light yellow platelets; m. p. 154.5–155° (vac.); the melt solidified and remelted at 176.5–178.5° to a cloudy liquid which became perfectly clear at 181°. It gave a blue-green color with an alcoholic solution of ferric chloride.

Anal. Calcd. for $C_{22}H_{16}O_3$: C, 80.5; H, 4.9. Found: C, 80.4; H, 5.1.

The keto ester (0.2 g.) was converted to its sodio derivative in 5 cc. of benzene by means of sodium methoxide, methyl iodide was added in portions (0.9 cc. in all), the mixture was allowed to remain at room temperature for two hours and then refluxed for two hours. The methylated product was heated with a mixture of 10 cc. of acetic acid, 5 cc. of concentrated hydrochloric acid and 1 cc. of water for four hours, the solvents were evaporated and the residue was dissolved in benzene. The solution was washed with dilute ammonium hydroxide, dried and passed through a short tower of alumina; from the solution 55 mg. (33%) of practically pure ketone was obtained. After one recrystallization from benzene it formed pale-yellow rhombs; m. p. 178–178.5° (vac.), alone and when mixed with the ketone obtained in (a).

3'-Methyl-3,4-benzpyrene.—One-half gram of the aforementioned ketone was reduced by means of a solution of aluminum isopropoxide and the crude chalk-white alcohol (0.47 g.) was heated with 50 mg. of palladium-charcoal catalyst at 300–320° as described. The pale-yellow product (0.42 g.; m. p. 142–145°), after evaporative distillation at 220° and 0.01 mm. pressure, crystallized from benzene-petroleum ether in fine needles; m. p. 147.5–148°, cor., with slight previous softening (reported,² 146.5–147°, cor., when heated slowly, and 147.6–148.1°, cor., on remelting). The picrate formed dark reddish-brown crystals in benzene-petroleum ether; m. p. 179–180°, cor. (reported,² 179.5–180°, cor.). The trinitrobenzene complex crystallized from benzene-petroleum ether in brilliant red

needles; m. p. 212.5–213°, cor. (reported,² 210.5–211°, cor.).

3',4'-Dimethyl-3,4-benzpyrene (XII).—One gram of 3'-methyl-4'-ketotetrahydrobenzpyrene in 10 cc. of dry benzene was added to a solution of methylmagnesium iodide prepared from 0.66 cc. of methyl iodide in 10 cc. of ether. The product obtained by hydrolysis of the mixture after three hours of refluxing was heated with 0.1 g. of palladium-charcoal catalyst at 300–320° for thirty minutes as described. The hydrocarbon which was obtained by sublimation from the catalyst at 0.01 mm. pressure was practically pure 3',4'-dimethyl-3,4-benzpyrene; yield, 0.85 g. (91%); m. p. 215–216°. From benzene it crystallized in yellow rhombic plates with no change in its melting point.

Anal. Calcd. for $C_{22}H_{16}$: C, 94.3; H, 5.7. Found: C, 94.7; H, 5.8.

The picrate crystallized from benzene in brown needles; m. p. 205–205.5°.

Anal. Calcd. for $C_{22}H_{16} \cdot C_6H_3N_3O_7$: N, 8.3. Found: N, 8.3.

Preparation of 3-Acylpyrenes.—The procedure employed for the preparation of these ketones is illustrated by the preparation of 3-acetylpyrene. Anhydrous aluminum chloride (66 g.) was dissolved in 200 cc. of nitrobenzene contained in a three-necked flask equipped with a mercury-sealed Hershberg stirrer and a thermometer. To the cooled solution was added 26 cc. of acetic anhydride, the mixture was cooled to –5°, and 50 g. of finely divided pyrene was added with efficient stirring in the course of about ten minutes. After three hours of stirring at 10° and four additional hours at 0° (for the reaction with isovaleric anhydride six hours in ice-salt mixture and six hours at room temperature were allowed), the mixture was hydrolyzed, the nitrobenzene was removed by steam distillation, and the ketone was distilled at 1 mm. pressure and recrystallized from methanol with the use of Norit. The yields and properties of the ketones are shown in the table; all of the ketones were obtained as yellow crystals.

TABLE I

$RCOC_6H_5$ R	3-ACYLPYRENES		Crystalline form
	Yield, %	M. p., °C.	
Methyl ^a	88	89–90	Plates
Ethyl ^b	85	79–80	Rhomb
n-Propyl ^c	85	73–74	Prisms
Isopropyl ^d	82	87–89	Leaflets
Isobutyl ^e	85	82–82.5	Platelets

^a Previously prepared from pyrene, acetic acid and zinc chloride⁶ (m. p. 90°) and from pyrene, acetyl chloride and aluminum chloride⁹ (m. p. 94°). ^b Prepared previously in 82% yield (m. p. 84–85°) by means of propionyl chloride.¹⁰ ^c *Anal.* Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9. Found: C, 87.9; H, 6.0. ^d *Anal.* Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9. Found: C, 87.7; H, 5.9. ^e *Anal.* Calcd. for $C_{21}H_{18}O$: C, 88.1; H, 6.3. Found: C, 88.6; H, 6.4.

The Willgerodt Reaction.—Following the procedure of Fieser and Kilmer,⁵ 2-g. samples of the ketones were sub-

(8) Cook and Hewett, *J. Chem. Soc.*, 398 (1933); Fieser and Novello, *This Journal*, **62**, 1855 (1940); Bachmann, Carmack and Safir, *ibid.*, **63**, 1682 (1941).

(9) Dziewoński and Sternbach, *Roczniki Chem.*, **17**, 101 (1937).

(10) Dziewoński and Trześciński, *Bull. intern. acad. polon. sci., Classe sci. math. nat.*, 579 (1937A).

jected to the action of ammonium polysulfide. From the cooled mixture obtained from 3-acetylpyrene, 1.95 g. (92%) of golden-brown centimeter-long prisms of practically pure **3-pyrenylacetamide** was filtered off and washed with a mixture of dioxane and ammonium polysulfide solution; m. p. 244–246°. A sample after sublimation at 240° and 0.01 mm. pressure crystallized from acetic acid–chlorobenzene in fine, colorless prismatic needles; m. p. 246–247°.

*Anal.*¹¹ Calcd. for $C_{18}H_{13}ON$: N, 5.41. Found: N, 5.39.

The unrecrystallized amide (13.7 g.) was dissolved in 200 cc. of boiling acetic acid, 100 cc. of concentrated hydrochloric acid was added cautiously through the top of the upright condenser attached to the flask, and the mixture was refluxed for one and one-quarter hours, when an additional 100 cc. of hydrochloric acid was added in order to precipitate the product. From the chilled mixture, the **3-pyrenylacetic acid** (13.4 g.; m. p. 218.5–220°) was filtered; it was purified through its water-soluble potassium salt and then recrystallized from chlorobenzene (130 cc.). The first crop of fine, slightly colored plates and prisms weighed 12.3 g. (90%); m. p. 222.5–223° (vac.) (reported,⁶ 220°, dec.).

The same acid was obtained in poor yield by heating a mixture of 3-chloromethylpyrene (prepared from 3-pyrenylcarbinol and phosphorus trichloride) and potassium cyanide in methanol for one and one-half hours, followed by refluxing the nitrile with 20% alcoholic potassium hydroxide for twenty-two hours.

The amide (1.7 g.; m. p. 177–181°) obtained from 2 g. of

3-propionylpyrene was hydrolyzed in the manner described and the acid was purified through its salt. The **β -3-pyrenylpropionic acid** (1.42 g.; m. p. 173–174°) crystallized from acetic acid–chlorobenzene in pale tan platelets; m. p. 178–179°. It can be obtained colorless by sublimation at 0.01 mm. pressure. The same acid was obtained from 3-chloromethylpyrene through the malonic ester synthesis.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.2; H, 5.1. Found: C, 83.1; H, 5.2.

The methyl ester was prepared by means of diazomethane; after evaporative distillation at 0.01 mm. pressure and recrystallization from methanol, it formed gleaming, colorless leaflets; m. p. 95.5–96.5°, cor. (reported,¹² 81°).

A 46% yield of **γ -3-pyrenylbutyric acid** was obtained as practically colorless crystals by hydrolysis of the 1.22 g. of crude amide (m. p. 172–175°) which was obtained from 2 g. of 3-*n*-butyrylpyrene; after recrystallization from a mixture of benzene, acetone and acetic acid, it melted at 186–187°, alone and when mixed with an authentic specimen.

Summary

The synthesis of the new 1'-methyl-3,4-benzopyrene from 3-acetylpyrene and new syntheses of 2'-methyl- and 3'-methyl-3,4-benzopyrene are described. 3',4'-Dimethyl-3,4-benzopyrene also has been synthesized.

A study has been made of the Willgerodt reaction on five 3-acylpyrenes.

ANN ARBOR, MICHIGAN

RECEIVED JULY 11, 1941

(11) Micronalysis by Torsti Salo.

